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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/500,747	02/09/2000	Rajesh S. Gokhale	300622004600	3023

7590 02/12/2002

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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	19

DATE MAILED: 02/12/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/500,747	Applicant(s) GOKHALE ET AL.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-44* is/are pending in the application.

4a) Of the above claim(s) *40-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *23-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,11,12*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement Paper No. 9 mailed on October 16, 2001, Applicants filed an election of invention (see below).

Election

2. Applicants' election without traverse of Group I, Claims 23-39 in Paper No. 10 is acknowledged. Claims 23-44 are pending in the instant application. Claims 40-44 are withdrawn from further consideration as non-elected inventions. Claims 23-39 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the U.S. Provisional Application No. 60/119,363 filed on February 9, 1999 as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statement filed on December 18, 2000 (Paper No. 4) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

5. The information disclosure statement filed on March 21, 2001 (Paper No. 5) fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign

patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following references were not considered for the reasons described below:

a) Other Document 2: No complete copy of Bohm *et al.* has been received.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

6. The information disclosure statement filed on May 9, 2000 (Paper No. 11) fails to comply with 37 C.F.R. § 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The following references were not considered for the reasons described below:

a) Other Documents 16-23: No copies have been received.

All other documents in said Information Disclosure statement were considered as noted by the Examiner initials in the copy attached hereto.

7. The information disclosure statement filed on September 20, 2001 (Paper No. 12) has been reviewed, and its references have been considered as shown by the Examiner's initials next to each citation on the attached copy.

8. The Examiner notes that, in total, Applicants have filed 142 references in the information disclosure. The Examiner would appreciate any *particular* relevancy Applicants can point out in the references.

Drawings

9. On September 20, 2001, Applicants filed a request for drawings correction; said correction to Figure 3 has been entered. Previously, the drawings (Figures 1-3) had been approved by the draftsman. However, new Figure 3 is considered informal for the reasons detailed in the attached copy of PTO Form 948. Appropriate correction to Figure 3 is required.

Compliance with the Sequence Rules

10. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. § 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

a) No paper copy of the sequence listing has been amended into the specification. The copy received on September 20, 2001 had no amendment directions for the specification. Moreover, no statement that the computer readable form and the paper copy were the same and that no new matter accompanied the filing.

Applicants must provide (1) a substitute copy of the sequence listing in paper copy, (2) an amendment directing its entry into the specification, and (3) a statement that the content of the paper copy filed therein and CRF filed on September 21, 2002 are the same and include no new matter as required by 37 C.F.R. § 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d).

Objections to the Specification

11. The specification is objected to for being incomplete. On page 15, line 6, a blank is found where the publication year of Jacobsen *et al.* belongs. The Examiner notes that this paragraph was amended on September 20, 2001. Appropriate correction is required.

12. The specification is objected to for being confusing. Throughout the specification, there are references that have been incorporated. Since the instant invention draws from many PKSs and their modular make-up, it would be useful to include, perhaps in drawing form, the modular construction of the PKSs specifically referred to, such as erythromycin, rifamycin, rapamycin, tylosin, narbonomycin, niddamycin, spiramycin, FK-520, and FK-506. Particularly since the instant invention requires knowledge of the native modular structure, i.e., whether the third module of FK-520 is at the beginning of a polypeptide (having an N-terminal ERL) or in the middle (having a RAL), such a drawing would be very helpful to one of skill in the art. Such a drawing must contain specification citation from the incorporated references.

13. The Abstract is objected to. The last sentence in the paragraph is confusing. Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

14. Claims 23-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant

regards as the invention. The metes and bounds of the intervening sequences that Applicants name **intra-molecular linkers (RAL)** and the N-terminal sequences that Applicants name **inter-molecule linkers (ERL)** are unclear.

From the specification (page 9 and Figure 3), the only consensus residue in a 16-20-residue RAL appears to be a *single* proline. The consensus sequence of an N-terminal ERL contains very vague and broad homologies over 32-40 amino acids (double a RAL) based on acidity and basicity of residues without particular definition of the location of these residues. Thus, using these homologies alone, one of skill in the art could not define the metes and bounds of the claimed RALs and ERLs. Additionally, in art-defined PKS sequences, the modules noted do not leave these large gaps (to fit in a RAL, for example) between modules. For example, in GenBank Accession Number M63676 defining the first open reading frame of the DEBS PKS (modules 1 and 2 – in between which should be a RAL as defined by Applicants), base pairs 744-6659 describe the "approximate span of module 1" and base pairs 6678-11219 describe the "approximate span of module 2"; these descriptions leave only 18 (=6678-6659) intervening base pairs which are equivalent to 6 amino acids, not 16-20 residues of a RAL. It is wholly unclear where the extra amino acids for the RAL come from.

In Claims 25 and 26, are these sequences intended to be those as exactly found in Figure 3? If so, these names should be replaced with the appropriate SEQ ID NOs as described in Figure 3. If not, particularly M2*rif*, M5*rif*, and M3*rap* are confusing since these modules have other modules covalently bound on their N and C terminal sides (they are one of at least three modules in an open reading frame, and they are in the middle), and it is unclear which side the RAL is found on.

15. Claims 23-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claim 23, line 3, the phrases "**a** C-terminus" and "**an** N-terminus" (emphasis added) are unclear since every polypeptide modules has only one C-terminus and one N-terminus. These articles should be replaces with the article ---the--- for clarity.

16. Claims 28-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In each of the instant claims, a span of modules is noted – for example, in Claim 28, modules 3-6 of the *ery* PKS are indicated. It is unclear whether these modules must be ordered 3-4-5-6 or whether they must only all be present in any particular order among themselves.

17. Claims 28-39 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The use of loading modules is well documented in the art as being used as the primer for productive polyketide production using polyketide synthases for biosynthesis. No mention of using loading modules is made in the instant claims. Such modules seem to be a required component of PKSs. Explanation is required.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

18. Claims 23-39 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to hybrid PKSs that contain RAL or ERL portions from *any* PKS.

To satisfy the written description aspect of 35 U.S.C. § 112, first paragraph, for a claimed genus of molecules, it must be clear that: (1) the identifying characteristics of the claimed molecules have been disclosed, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these; and (2) a representative number of species within the genus must be disclosed.

The specification describes RALs and ERLs as found in the *ery* PKS, the *rif* PKS, and the *rap* PKS (see Figure 3). The structure/function relationship described on page 9 and in Figure 3 do not describe sufficiently identifying characteristics of these claimed RALs and ERLs to support claims to the entire genus of molecules. See also the discussion above concerning the confusing nature of the definition of RALs and ERLs. Thus, the instant claims lack adequate written description.

19. Claims 28-39 are rejected under 35 U.S.C. 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to hybrid PKS modules comprising modules from specific PKSs known in the art. However, no description of the modular structure of said PKSs is described.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

The instant claims are drawn to hybrid PKSs comprising specific modules of tylosin, narbonomycin, spiramycin, niddamycin, FK-520, FK-506, and rapamycin PKSs. The modular structure, while taught in the art, is not described in the instant specification. To simply understand the instant claims, one of skill in the art must compile information from several

different sources to understand the character of the modules claimed. For example, does module 5 of the tylosin PKS begin with a portion of a RAL or with an ERL? This lack of description of the modular structures of the PKSs whose modules are used in the hybrid PKSs claimed is a clear deficiency in the description. Moreover, none of the claimed hybrid PKSs would seem to be in the possession of the inventors as based on the examples which *only* utilize RALs and ERLs from DEBS and only utilize DEBS modules and one rifamycin module.

20. Claims 23-26 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for hybrid PKSs that facilitate transfer from a first module to a second module, does not reasonably provide enablement for hybrid PKSs that do not facilitate transfer from a first module to a second module. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The instant claims clearly encompass such scope as evidenced by the further limiting Claim 27 that adds this limitation. To use such hybrid PKSs would require undue experimentation on the art of one of skill in the art.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of

experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

The instant specification only provides working examples for functioning hybrid PKSs – that is, those which produce some form of polyketide by transferring a nascent polyketide chain from one module to another. It would require copious amounts of unguided experimentation to identify other uses of the claimed hybrid PKSs. The state of the prior art is that only functional PKSs are used to produce polyketides; no other functions are evident in the art. It is wholly unpredictability how non-functional hybrid PKS can be used. Thus, the full extent of the scope of the instant claims lacks enablement.

21. Claims 23-39 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for functional hybrid PKSs using RALs and/or ERLs from the DEBS PKS, does not reasonably provide enablement for functional hybrid PKSs using RALs and/or ERLs from **other** PKSs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention

commensurate in scope with these claims. To utilize RALs and ERLs from any PKS would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

The working examples offered in the specification utilize RALs and ERLs from **ONLY** DEBS. Except for one example (Example 5), the modules used are *exclusively* DEBS modules. Examples 3-5, while being able to produce polyketides from their hybrid constructs, offer no controls in the experiments. Can these linker regions be predictably identified and utilized with *all* modules from *any* modular PKS? While the state of the prior art has shown great predictability among modular PKSs, the limited homology of the "linker" regions, as identified by Applicants in the instant specification, does not support such broad generalities. The teachings of Tang *et al.* (Chem. Biol. (2000) 7:77-84) demonstrate that combinations of modules from different PKSs (pikromycin, erythromycin, and oleandomycin) without the use of ERLs as Applicants. The unpredictability of the experimentation required of one of skill in the art to make and effectively use the invention, in addition to the lack of examples and the state of the prior art, render such experimentation undue. Thus, the full extent of the claimed scope is not enabled.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

22. Claims 23, 25, 26, and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by McDaniel *et al.* (IDS #4, reference #7). The instant claims are drawn to a hybrid PKS comprised of a first extender module and a second extender module linked via a RAL that is M6 *ery* wherein the first extender module (or the second) is not covalently linked to the RAL naturally. Claim 26 is included in the instant rejection because, while Claim 26 limits the ERL, the RAL can still be utilized, instead of the ELR, and meet the limitations of the claim as set forth in Claim 23.

McDaniel *et al.* teach a PKS wherein "the ACP2 and KS3 boundaries are connected by the intermodule segments originally connecting DEBS modules 5 and 6" (see page 670, left column and Figures 4 and 5). Thus, McDaniel *et al.* teach the RAL (Applicants' term) between DEBS modules 5 and 6 now located between DEBS modules 2 and 3.

23. Claims 23, 25, 26, and 27 are rejected under 35 U.S.C. § 102(a) as being anticipated by Ranganathan *et al.* (IDS #11, reference #21). The instant reference, published in October, 1999, is an intervening reference between Applicants' provisional filed in February, 1999, and the instant application filed in February, 2000. Due to the questions of enablement presented above,

and the fact that additional experimentation was added to the provisional for the instant application to be complete, the instant rejection is set forth.

Ranganathan *et al.* teach TKS-AR3 which uses an alternate KS domain to productively connect DEBS module 1 and rap module 12 (see Figure 3). Ranganathan *et al.* also teach using the ACP domain of module 2 (DEBS) to mediate the transfer of the polyketide chain between modules 1 and 3 (see Figure 3, TKS-JC1 and page 736, right column). Thus, this teaching uses alternate linkers to facilitate hybrid PKS construction.

Conclusion

24. Claims 23-39 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm. If attempts to reach the examiner are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-0294 for regular communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

KMK
February 8, 2002

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